WEST Search History

Hide Items | Restore | Clear | Cancel

DATE: Friday, June 02, 2006

Hide?	Set Name	Query	Hit Count
	DB=PGPB,USPT; PLUR=YES; OP=OR		
☐	L8	L7 and (neutrophil? or PMN)	109
☐	L7	L6 and apoptosis	538
☐	L6	(inositol adj 1 adj 4 adj 5 adj triphosphate adj 3 adj kinase adj C or ITPKC or PI3 adj kinase)	913
	DB=EPAB,JPAB,DWPI; PLUR=YES; OP=OR		
☐	L5	((inositol adj 1 adj 4 adj 5 adj triphosphate adj 3 adj kinase adj C or ITPKC or PI3 adj kinase))	63

END OF SEARCH HISTORY

WEST Search History

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DATE: Friday, June 02, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT; PLUR=YES; OP=OR	
☐	L4	MURPHY adj FINBARR	3
☐	L3	HAYES adj IAN	6
☐	L2	HAYES adj IAN	6
☐	L1	SEERY adj LIAM	4

END OF SEARCH HISTORY

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 NEWS  3  JAN 17   Pre-1988 INPI data added to MARPAT
 NEWS  4  FEB 21   STN AnaVist, Version 1.1, lets you share your STN AnaVist
                   visualization results
 NEWS  5  FEB 22   The IPC thesaurus added to additional patent databases on STN
 NEWS  6  FEB 22   Updates in EPFULL; IPC 8 enhancements added
 NEWS  7  FEB 27   New STN AnaVist pricing effective March 1, 2006
 NEWS  8  MAR 03   Updates in PATDPA; addition of IPC 8 data without attributes
 NEWS  9  MAR 22   EMBASE is now updated on a daily basis
 NEWS 10  APR 03   New IPC 8 fields and IPC thesaurus added to PATDPAFULL
 NEWS 11  APR 03   Bibliographic data updates resume; new IPC 8 fields and IPC
                   thesaurus added in PCTFULL
 NEWS 12  APR 04   STN AnaVist $500 visualization usage credit offered
 NEWS 13  APR 12   LINSPEC, learning database for INSPEC, reloaded and enhanced
 NEWS 14  APR 12   Improved structure highlighting in FQHIT and QHIT display
                   in MARPAT
 NEWS 15  APR 12   Derwent World Patents Index to be reloaded and enhanced during
                   second quarter; strategies may be affected
 NEWS 16  MAY 10   CA/CAplus enhanced with 1900-1906 U.S. patent records
 NEWS 17  MAY 11   KOREAPAT updates resume
 NEWS 18  MAY 19   Derwent World Patents Index to be reloaded and enhanced
 NEWS 19  MAY 30   IPC 8 Rolled-up Core codes added to CA/CAplus and
                   USPATFULL/USPAT2
 NEWS 20  MAY 30   The F-Term thesaurus is now available in CA/CAplus

 NEWS EXPRESS      FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a,
                   CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
                   AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005.
                   V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT
                   http://download.cas.org/express/v8.0-Discover/

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FILE 'HOME' ENTERED AT 09:48:19 ON 02 JUN 2006

=> file medline embase biosis caplus
COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 0.21 | 0.21

FILE 'MEDLINE' ENTERED AT 09:48:38 ON 02 JUN 2006

FILE 'EMBASE' ENTERED AT 09:48:38 ON 02 JUN 2006

FILE 'BIOSIS' ENTERED AT 09:48:38 ON 02 JUN 2006

FILE 'CAPLUS' ENTERED AT 09:48:38 ON 02 JUN 2006

=> s (inositol adj 1 adj 4 adj 5 adj triphosphate adj 3 adj kinase adj C or ITPKC or PI3 adj kinase)
L1 11 (INOSITOL ADJ 1 ADJ 4 ADJ 5 ADJ TRIPHOSPHATE ADJ 3 ADJ KINASE ADJ C OR ITPKC OR PI3 ADJ KINASE)

=> inositol adj 1(w)4(w)5(w)triphosphate(w)3(w)kinase(w)C or ITPKC or PI3(w)kinase
INOSITOL IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s inositol adj 1(w)4(w)5(w)triphosphate(w)3(w)kinase(w)C or ITPKC or PI3(w)kinase
L2 9050 INOSITOL ADJ 1(W) 4(W) 5(W) TRIPHOSPHATE(W) 3(W) KINASE(W) C OR ITPKC OR PI3(W) KINASE

=> s l2 and apoptosis
L3 1756 L2 AND APOPTOSIS

=> s l3 and (neutrophil? or PMN)
L4 42 L3 AND (NEUTROPHIL? OR PMN)

=> dup rem l4
PROCESSING COMPLETED FOR L4
L5 25 DUP REM L4 (17 DUPLICATES REMOVED)

=> dis ibib abs l5 15-25

L5 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:458227 CAPLUS
DOCUMENT NUMBER: 141:223474
TITLE: Granulocyte **apoptosis**: who would work with a 'real' inflammatory cell?
AUTHOR(S): Dransfield, I.; Rossi, A. G.
CORPORATE SOURCE: MRC Centre for Inflammation Research, University of Edinburgh Medical School, Edinburgh, EH8 9AG, UK
SOURCE: Biochemical Society Transactions (2004), 32(3), 447-451
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The **neutrophil** granulocyte is a key factor in cellular innate defense mechanisms against infection or tissue damage. Granulocyte **apoptosis** is now acknowledged to have a critical role

in progression of inflammatory responses. Granulocytes are preprogrammed to die with important physiol. mechanisms for non-inflammatory clearance. Shutdown of secretory capacity represents an important aspect of the program of biochem. events that accompany **neutrophil apoptosis** together with surface mol. changes that serve to identify apoptotic cells as targets for phagocytic removal. Defining the underlying regulatory mechanisms together with the changes in patterns of gene/protein expression associated with granulocyte death remains a challenge. Use of novel strategies for inducing cell death will allow biochem. approaches to dissect the underlying pathways. Although study of granulocyte cell death has especial difficulties when compared with other cell types, there are clearly potential benefits for new therapeutic approaches to treat inflammatory diseases.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 6

ACCESSION NUMBER: 2005:130748 BIOSIS
DOCUMENT NUMBER: PREV200500122019
TITLE: The roles of **PI3-kinase** and PKC in the signaling pathways of human **neutrophil apoptosis** induced by Entamoeba histolytica.
AUTHOR(S): Sim, Seobo [Reprint Author]; Shin, Myeong Heon; Kim, Kyeong Ah; Ryu, Jae-Sook
CORPORATE SOURCE: Dept ParasitolInst Trop MedBrain Korea 21 Project Med Sci, Yonsei Univ, Seoul, 120749, South Korea
SOURCE: Journal of Leukocyte Biology Supplement, (2004) No. 2004, pp. 50. print.
Meeting Info.: 37th Annual Meeting of the Society for Leukocyte Biology "Host Response to Pathogens". Toronto, ON, Canada. October 21-23, 2004. Society for Leukocyte Biology.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 1 Apr 2005
Last Updated on STN: 1 Apr 2005

L5 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2003:454493 CAPLUS
DOCUMENT NUMBER: 139:31825
TITLE: Nucleic acid and polypeptide sequences for human 55-kilodalton phosphatidylinositol 3-kinase and their diagnostic and therapeutic uses for **apoptosis**
INVENTOR(S): Hayes, Ian; Cotter, Thomas; Murphy, Finbarr; Seery, Liam
PATENT ASSIGNEE(S): Eirx Therapeutics Limited, Ire.
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003048361	A2	20030612	WO 2002-GB5547	20021206
WO 2003048361	A3	20040318		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002347368	A1	20030617	AU 2002-347368		20021206
PRIORITY APPLN. INFO.:			GB 2001-29377	A	20011207
			GB 2002-831	A	20020115
			WO 2002-GB5547	W	20021206

AB The invention provides a method for detecting **apoptosis** in a cell comprising detecting an alteration in any one of: (i) a phosphatidylinositol kinase (p55PIK) polypeptide having an amino acid sequence as set out in SEQ ID NO:1; (ii) a polypeptide having at least 80 % homol. with (i); (iii) a nucleic acid encoding a polypeptide having the sequence set out in (i) or (ii); (iv) a nucleic acid which hybridizes under stringent conditions to the sequence set out in (iii); or (v) the complement of (iii) or (iv). The invention accordingly provides a method of modulating **apoptosis** by modulating p55PIK gene expression and a method for identifying genes associated with p55PIK gene expression and thus identifying other genes associated with **apoptosis**. The invention also provides a novel nucleic acid sequence encoding the promoter region for p55PIK gene. The invention further claims methods and compns. such as p55PIK siRNA, p55PIK antisense nucleic acids, and microarrays for use in identifying drug candidates that modulate p55PIK expression or activity. The methods are claimed for therapeutic use in treatment of cancer, inflammation, and neurodegenerative diseases. In the examples of the invention, the fungal metabolite gliotoxin was identified as an inhibitor of granulocyte macrophage colony-stimulating factor (GM-CSF)-mediated inhibition of human **neutrophil apoptosis**. An increase in p55PIK mRNA in GM-CSF-induced **neutrophil** survival is blocked by gliotoxin. The p55PIK gene and signal transduction-associated genes were differentially expressed in microarray expts. of **neutrophil apoptosis** and survival.

L5 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2003:398123 CAPLUS
DOCUMENT NUMBER:	140:35353
TITLE:	Alteration of constitutive **apoptosis** in **neutrophils** by quinolones
AUTHOR(S):	Azuma, Yasutaka; Ohura, Kiyoshi
CORPORATE SOURCE:	Department of Pharmacology, Osaka Dental University, Hirakata, Osaka, 573-1121, Japan
SOURCE:	Inflammation (Dordrecht, Netherlands) (2003), 27(3), 115-122 CODEN: INFLD4; ISSN: 0360-3997
PUBLISHER:	Kluwer Academic Publishers
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB **Neutrophils** constitutively undergo **apoptosis** at sites of infection. The process of **apoptosis** controls inflammatory responses of **neutrophils**. However, little is known about the abilities of quinolones, which are often administered to patients showing infection disease, on constitutive **apoptosis** of **neutrophils**. The aim of this study is to evaluate abilities of quinolones on constitutive **apoptosis** of **neutrophils**. Tosufloxacin delayed **neutrophil** death and delayed **neutrophil apoptosis**. In contrast, ofloxacin, lomefloxacin, fleroxacin, sparfloxacin, and levofloxacin markedly promoted **neutrophil** death without affecting **neutrophil apoptosis**. Inhibitors of phosphoinositide 3-kinase (PI3K) and p38 mitogen-activated protein kinase (MAPK) attenuated the delay of **neutrophil apoptosis** by tosufloxacin, resp. However, an inhibitor of extracellular-signal-related kinase did not alter the delay

of **neutrophil apoptosis** by tosufloxacin. Moreover, tosufloxacin increases the expression of p85, p110β, and Akt protein in **neutrophils**. These results suggest that tosufloxacin may delay **neutrophil apoptosis** via activation of PI3K/Akt and/or p38 MAPK, and the other quinolones may promote **neutrophil** death without affecting their **apoptosis**.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 19 OF 25 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2002477246 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12239175
TITLE: Role of **PI3-kinase**-dependent Bad phosphorylation and altered transcription in cytokine-mediated **neutrophil** survival.
AUTHOR: Cowburn Andrew S; Cadwallader Karen A; Reed Benjamin J; Farahi Neda; Chilvers Edwin R
CORPORATE SOURCE: Respiratory Medicine Division, Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge, United Kingdom.
SOURCE: Blood, (2002 Oct 1) Vol. 100, No. 7, pp. 2607-16. Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20 Sep 2002
Last Updated on STN: 19 Dec 2002
Entered Medline: 5 Dec 2002

AB Phosphoinositide 3-kinase (**PI3-kinase**)-dependent phosphorylation of the proapoptotic Bcl-2 family member Bad has been proposed as an important regulator of apoptotic cell death. To understand the importance of this pathway in nontransformed hematopoietic cells, we have examined the effect of survival cytokines on **PI3-kinase** activity and Bad expression and phosphorylation status in human **neutrophils**. Granulocyte macrophage-colony-stimulating factor (GM-CSF) and tumor necrosis factor-alpha (TNF-alpha) both reduced the rate of **apoptosis** in **neutrophils** cultured in vitro for 20 hours. Coincubation with the **PI3-kinase** inhibitor LY294002, which in parallel experiments abolished GM-CSF-primed, fMLP-stimulated superoxide anion production and GM-CSF-stimulated PtdIns(3,4,5)P(3) accumulation, inhibited the GM-CSF and TNF-alpha survival effect. In contrast, the MAP kinase kinase (MEK1/2) inhibitor PD98059 and the protein kinase A inhibitor H-89 had only a marginal effect on GM-CSF-mediated **neutrophil** survival. GM-CSF substantially increased Bad phosphorylation at Ser112 and Ser136 and increased the cytosolic accumulation of Bad. GM-CSF also regulated Bad at a transcription level with a marked decrease in mRNA levels at 4 hours. TNF-alpha caused a biphasic effect on the rate of morphologic **apoptosis**, which corresponded to an early increase, and a late inhibition, of Bad mRNA levels. LY294002 inhibited GM-CSF- and TNF-alpha-mediated changes in Bad phosphorylation and mRNA levels. These data suggest that the survival effect of GM-CSF and TNF-alpha in **neutrophils** is caused by a **PI3-kinase**-dependent phosphorylation and cytosolic translocation of Bad, together with an inhibition of Bad mRNA levels. This has important implications for the regulation of **neutrophil apoptosis** in vivo.

L5 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:109306 CAPLUS
DOCUMENT NUMBER: 136:261789
TITLE: Acute endotoxemia prolongs the survival of rat lung

neutrophils in response to 12-O-tetradecanoyl-phorbol 13-acetate

AUTHOR(S): Sunil, Vasanthi R.; Connor, Agnieszka J.; Lavnikova, Natasha; Gardner, Carol R.; Laskin, Jeffrey D.; Laskin, Debra L.

CORPORATE SOURCE: Department of Pharmacology and Toxicology, Rutgers University, Piscataway, NJ, 08854, USA

SOURCE: Journal of Cellular Physiology (2002), 190(3), 382-389
CODEN: JCLLAX; ISSN: 0021-9541

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Acute endotoxemia is associated with prolonged survival of adherent **neutrophils** in the lung vasculature. In the present studies, the effects of inflammatory mediators on signaling pathways regulating **neutrophil** survival were examined We found that the protein kinase C activator, 12-O-tetradecanoyl-phorbol 13-acetate (TPA), but not interferon-γ (IFN-γ), prolonged the survival of adherent vasculature lung **neutrophils** from endotoxemic rats, a response that was correlated with reduced **apoptosis**. Although endotoxin administration to rats induced the expression of the anti-apoptotic protein Mcl-1 in lung **neutrophils**, TPA had no effect on this response. Endotoxin administration also induced expression of total p38 and p44/42 mitogen activated protein kinases (MAPK) in **neutrophils** , as well as phosphatidyl inositol 3 kinase (PI3K) and its downstream target protein kinase B (PKB). Treatment of the cells with TPA increased p38 MAPK expression in cells from both control and endotoxin treated animals. Cells from endotoxin treated, but not control animals, were found to exhibit constitutive binding activity of nuclear factor kappa B (NF-κB) which was blocked by TPA. In contrast, constitutive CCAAT/enhancer binding protein (C/EBP) nuclear binding activity evident in **neutrophils** from control animals was reduced following endotoxin administration. Moreover, this response was independent of TPA. These data suggest that NF-κB plays a role in TPA-induced signaling leading to prolonged survival of adherent vascular **neutrophils** in the lung during acute endotoxemia.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:541555 CAPLUS

DOCUMENT NUMBER: 137:153784

TITLE: Polysaccharide purified from Ganoderma lucidum inhibits spontaneous and Fas-mediated **apoptosis** in human **neutrophils** through activation of the phosphatidylinositol 3 kinase/Akt signaling pathway

AUTHOR(S): Hsu, Ming-Jen; Lee, Shiuh-Sheng; Lin, Wan-Wan

CORPORATE SOURCE: Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan

SOURCE: Journal of Leukocyte Biology (2002), 72(1), 207-216
CODEN: JLBIE7; ISSN: 0741-5400

PUBLISHER: Federation of American Societies for Experimental Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Ganoderma lucidum has been widely used as a remedy to promote health and longevity in China. The polysaccharide component with a branched (1→3)-β-D-glucan moiety from G. lucidum (PS-G) has shown evidence of enhancement of immune responses and of eliciting anti-tumor effects. In this study, the authors investigated the effect of PS-G on **neutrophil** viability, which is manifested by spontaneous **apoptosis**. Annexin V staining and MTT assays reveal that PS-G is able to inhibit spontaneous and Fas-induced **neutrophil**

apoptosis, and this effect of PS-G is enhanced by the presence of zVAD (a caspase inhibitor) and GM-CSF. The anti-apoptotic effect of PS-G is diminished by the presence of wortmannin and LY294002 (two PI-3K inhibitors), but is not altered by PD98059 (a MEK inhibitor). Western blotting indicates the stimulating effect of PS-G on Akt phosphorylation and its inhibition of procaspase 3 degradation, which occurs in **neutrophils** undergoing spontaneous **apoptosis** or triggered death by Fas. Taken together, PS-G elicitation of antiapoptotic effects on **neutrophils** primarily relies on activation of Akt-regulated signaling pathways.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 25 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2002193291 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11926309
TITLE: CPPD crystal-induced suppression of **neutrophil apoptosis** is regulated by the ERK1/2 and **PI3-kinase**/Akt pathways.
AUTHOR: Tudan C; Jackson J K; Burt H M
CORPORATE SOURCE: Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, Canada.. tudanc@shaw.ca
SOURCE: Inflammation research : official journal of the European Histamine Research Society ... [et al.], (2002 Feb) Vol. 51, No. 2, pp. 105-7.
Journal code: 9508160. ISSN: 1023-3830.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 4 Apr 2002
Last Updated on STN: 28 Sep 2002
Entered Medline: 27 Sep 2002

L5 ANSWER 23 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2003:52162 BIOSIS
DOCUMENT NUMBER: PREV200300052162
TITLE: Acquisition of an apoptotic phenotype by retinoic acid-matured HL-60 cells in **PI3-kinase** -dependent.
AUTHOR(S): Jia, Song Hui [Reprint Author]; Parodo, Jean [Reprint Author]; Marshall, John C. [Reprint Author]
CORPORATE SOURCE: Department of Surgery, University of Toronto, Toronto, ON, Canada
SOURCE: Journal of Interferon and Cytokine Research, (2002) Vol. 22, No. Supplement 1, pp. S-156. print.
Meeting Info.: Joint Meeting of the International Society for Interferon and Cytokine Research, the International Cytokine Society, the Society for Leukocyte Biology, and the European Cytokine Society on Cytokines and Interferons. Turin, Italy. October 06-10, 2002. International Society for Interferon and Cytokine Research.
ISSN: 1079-9907 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jan 2003
Last Updated on STN: 22 Jan 2003

L5 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:885681 CAPLUS
DOCUMENT NUMBER: 136:31664

TITLE: Compositions and methods for identifying agents which modulate PTEN function and PI-3 kinase pathways

INVENTOR(S): Durden, Donald L.

PATENT ASSIGNEE(S): Advanced Research & Technology Institute, USA

SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001091699	A2	20011206	WO 2001-US17358	20010530
WO 2001091699	A3	20021227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2410514	AA	20011206	CA 2001-2410514	20010530
AU 2001065137	A5	20011211	AU 2001-65137	20010530
US 2002150954	A1	20021017	US 2001-870379	20010530
US 6777439	B2	20040817		
EP 1289472	A2	20030312	EP 2001-939641	20010530
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2005032727	A1	20050210	US 2003-712850	20031113
US 2004142395	A1	20040722	US 2004-770725	20040203

PRIORITY APPLN. INFO.:

US 2000-208437P	P	20000530
US 2001-274167P	P	20010308
US 2001-870379	A1	20010530
WO 2001-US17358	W	20010530

AB Methods are provided for the identification, biochem. characterization and therapeutic use of agents which impact PTEN, p53, PI-kinase and AKT mediated cellular signaling. The present invention provides methods for the treatment of cancer associated with PTEN mutation. Exemplary methods include delivery of a native PTEN encoding nucleic acid to cancer cells such that the native PTEN protein is expressed. Addnl. methods for the treatment of cancer in accordance with the present invention entail the administration of at least one agent selected from the group consisting of PTEN agonists, **PI3 kinase** inhibitors and AKT inhibitors. The aforementioned treatment protocols may also comprise the administration of conventional chemotherapeutic agents. In another aspect of the invention, methods for the prevention of aberrant angiogenesis are also provided. Methods for the administration of at least one agent selected from the group consisting of native PTEN encoding nucleic acids, PTEN agonists, PI3kinase inhibitors and AKT inhibitors for the inhibition or prevention of aberrant angiogenesis are also disclosed herein. PTEN has also been implicated in immunoreceptor modulation. Thus, in yet another aspect of the invention, methods for inhibiting the immune response in target cells are provided. In yet another aspect of the invention, methods for regulating p53 mediated gene expression are also provided. Such methods entail the administration of native PTEN, PTEN agonists and/or **PI3 kinase** inhibitors or AKT inhibitors to induce functional p53 in tumor cells. Given the widespread effects of PTEN, methods for identifying agents which modulate PTEN activity are also provided. Also provided in accordance with the present invention are high throughput screening methods for identifying small mols. which have affinity for PTEN or fragments thereof.

L5 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:824537 CAPLUS
DOCUMENT NUMBER: 136:367504
TITLE: Bacterial lipoprotein activates nuclear factor kappa B and delays **neutrophil apoptosis** via a pathway involving p38 MAP kinase and **PI3 kinase**
AUTHOR(S): Manning, Brian J.; Wang, Jiang Huai; Redmond, H. Paul
CORPORATE SOURCE: Department of Academic Surgery, Cork University Hospital and University College Cork, Cork, Ire.
SOURCE: Surgical Forum (2001), 52, 167-168
CODEN: SUFOAX; ISSN: 0071-8041
PUBLISHER: American College of Surgeons
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of bacterial lipoprotein (BLP) on **neutrophil** activation was examined by assessing nuclear factor kappa B activation and apoptotic rate over a 24-h period. The BLP activated NFκB in human **neutrophils**, and the time course of this activity was comparable to that of lipopolysaccharide, with maximal activation seen at 30 min. It also increased the nuclear translocation of the p65 subunit and induced a delay in **apoptosis** that was dependent on the p38 MAP kinase and the **PI3 kinase** pathways. NFκB inhibition and JNK inhibition did not affect the apoptotic rates of unstimulated **neutrophils** or of those treated with BLP. The inhibition of p38 MAP kinase also decreased the BLP-induced apoptotic delay assessed at 24 h to within normal limits.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> dis ibib abs l5 1-14

L5 ANSWER 1 OF 25 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2006045169 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16223772
TITLE: Interaction between integrin alpha9beta1 and vascular cell adhesion molecule-1 (VCAM-1) inhibits **neutrophil apoptosis**.
AUTHOR: Ross Ewan A; Douglas Mike R; Wong See Heng; Ross Emma J; Curnow S John; Nash Gerard B; Rainger Ed; Scheel-Toellner Dagmar; Lord Janet M; Salmon Mike; Buckley Christopher D
CORPORATE SOURCE: Division of Immunity and Infection, Medical Research Council (MRC) Centre for Immune Regulation, Institute for Biomedical Research, University of Birmingham, United Kingdom.
SOURCE: Blood, (2006 Feb 1) Vol. 107, No. 3, pp. 1178-83. Electronic Publication: 2005-10-13. Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 26 Jan 2006
Last Updated on STN: 3 Mar 2006
Entered Medline: 2 Mar 2006
AB According to the prevailing paradigm, **neutrophils** are short-lived cells that undergo spontaneous **apoptosis** within 24 hours of their release from the bone marrow. However, **neutrophil** survival can be significantly prolonged within inflamed tissue by cytokines, inflammatory mediators, and hypoxia. During screening experiments aimed at identifying the effect of the adhesive

microenvironment on **neutrophil** survival, we found that VCAM-1 (CD106) was able to delay both spontaneous and Fas-induced **apoptosis**. VCAM-1-mediated survival was as efficient as that induced by the cytokine IFN-beta and provided an additive, increased delay in **apoptosis** when given in combination with IFN-beta. VCAM-1 delivered its antiapoptotic effect through binding the integrin alpha9beta1. The alpha9beta1 signaling pathway shares significant features with the IFN-beta survival signaling pathway, requiring **PI3 kinase**, NF-kappaB activation, as well as de novo protein synthesis, but the kinetics of NF-kappaB activation by VCAM-1 were slower and more sustained compared with IFN-beta. This study demonstrates a novel functional role for alpha9beta1 in **neutrophil** biology and suggests that adhesive signaling pathways provide an important extrinsic checkpoint for the resolution of inflammatory responses in tissues.

L5 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:78074 CAPLUS
DOCUMENT NUMBER: 142:172874
TITLE: **Apoptosis**-related kinase/G protein-coupled receptors and their use in diagnosis and drug screening
INVENTOR(S): Seery, Liam; Hayes, Ian; Murphy, Finbarr
PATENT ASSIGNEE(S): Eirx Therapeutics Limited, Ire.
SOURCE: U.S. Pat. Appl. Publ., 264 pp., Cont.-in-part of U.S. Ser. No. 764,238.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005019746	A1	20050127	US 2004-781581		20040218
US 2004219616	A1	20041104	US 2004-764238		20040123
PRIORITY APPLN. INFO.:			GB 2003-1566	A	20030123
			US 2003-457533P	P	20030325
			US 2004-764238	A2	20040123

AB The present invention relates to methods of identifying an agent that modulates the function of an **apoptosis**-associated polypeptide. RNA interference (siRNA knockdown) in the **neutrophil** model of **apoptosis** identify the following kinases and/or G protein-coupled receptors (GPCR) as having roles in **apoptosis**: MAK, GPR86, PCTAIRE, GRAF, MPSK1, RS6PK, TLK2, EK1, MKNK, NTKL, CDC42, RBSK, EDG6, PRK, MAPKK5, P14KB, FLT4, PSKH1, **ITPKC**, and ROCK. The invention also relates to methods of modulating **apoptosis**, diagnostic methods, arrays, kits and compns. based upon the **apoptosis** -associated polypeptides.

L5 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:487619 CAPLUS
DOCUMENT NUMBER: 143:171209
TITLE: Apoptotic Pathways Are Inhibited by Leptin Receptor Activation in **Neutrophils**
AUTHOR(S): Bruno, Andreina; Conus, Sebastien; Schmid, Ines; Simon, Hans-Uwe
CORPORATE SOURCE: Department of Pharmacology, University of Bern, Bern, Switz.
SOURCE: Journal of Immunology (2005), 174(12), 8090-8096
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Leptin regulates food intake as well as metabolic, endocrine, and immune functions. It exerts proliferative and antiapoptotic activities in a variety of cell types, including T cells. Leptin also stimulates macrophages and **neutrophils**, and its production is increased during inflammation. In this study, we demonstrate that human **neutrophils** express leptin surface receptors under in vitro and in vivo conditions, and that leptin delays **apoptosis** of mature **neutrophils** in vitro. The antiapoptotic effects of leptin were concentration dependent and blocked by an anti-leptin receptor mAb. The efficacy of leptin to block **neutrophil apoptosis** was similar to G-CSF. Using pharmacol. inhibitors, we obtained evidence that leptin initiates a signaling cascade involving PI3K- and MAPK-dependent pathways in **neutrophils**. Moreover, leptin delayed the cleavage of Bid and Bax, the mitochondrial release of cytochrome c and second mitochondria-derived activator of caspase, as well as the activation of both caspase-8 and caspase-3 in these cells. Taken together, leptin is a survival cytokine for human **neutrophils**, a finding with potential pathol. relevance in inflammatory diseases.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 25 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2005205638 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15625305
TITLE: Activation of **PI3-kinase**/PKB contributes to delay in **neutrophil apoptosis** after thermal injury.
AUTHOR: Hu Zhihong; Sayeed Mohammed M
CORPORATE SOURCE: Dept. of Physiology, Loyola Univ. Medical Center, 2160 S. First Ave., Maywood, IL 60153, USA.. zhu1@luc.edu
CONTRACT NUMBER: R01GM-52325 (NIGMS)
R01GM-56865 (NIGMS)
SOURCE: American journal of physiology. Cell physiology, (2005 May) Vol. 288, No. 5, pp. C1171-8. Electronic Publication: 2004-12-29.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200506
ENTRY DATE: Entered STN: 21 Apr 2005
Last Updated on STN: 10 Jun 2005
Entered Medline: 9 Jun 2005

AB **Neutrophil apoptosis** is delayed under trauma and/or sepsis injury conditions. The molecular mechanism for the delay in **apoptosis** has not been well defined. We investigated whether activation of phosphatidyl inositol 3-kinase (**PI3-kinase**)/PKB signaling pathway contributes to the delay in **neutrophil apoptosis** with thermal injury. Rats were subjected to burns (30% total body surface area, 98 degrees C for 10 s), and euthanized 24 h later. Blood **neutrophils** were isolated with the use of Ficoll gradient centrifugation and cultured for the indicated time periods. **Apoptosis** was determined using annexin V and PI labeling and flow cytometry. NF-kappaB activation was examined using gel mobility shift assay and confocal microscopy. Expression levels of inhibitory **apoptosis** proteins (IAPs), including cellular IAP1 (cIAP1), cIAP2, X-linked IAP (XIAP), and survivin, and Bcl-2 family members such as Bcl-xl and Bad, were determined by Western blot analysis and/or RT-PCR, real-time PCR. The results showed that in culture, the decrease in **apoptosis** of **neutrophils** from thermally injured rats was prevented in the presence of **PI3-kinase** inhibitors wortmannin and LY-294002. There was upregulation of PKB and Bad

phosphorylation and NF-kappaB activation in N-formyl-l-methionyl-l-leucyl-l-phenylalanine-stimulated **neutrophils** from thermally injured rats compared with the sham injured group. Increased Bad phosphorylation and NF-kappaB activation were also attenuated by wortmannin. Bcl-xl expression in **neutrophils** was upregulated with thermal injury and inhibited in the presence of wortmannin. However, the expression of IAP family members was neither affected by thermal injury nor inhibited by wortmannin. These data suggest that the delay in **neutrophil apoptosis** with thermal injury is partly caused by activation of **PI3-kinase**/PKB signaling and NF-kappaB, which appeared to be related to the increased Bcl-xl expression and phosphorylation of Bad, but not IAP expression.

L5 ANSWER 5 OF 25 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2005222786 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15755871
TITLE: The effect of fever-like temperatures on **neutrophil** signaling.
AUTHOR: Salanova Birgit; Choi Mira; Rolle Susanne; Wellner Maren; Scheidereit Claus; Luft Friedrich C; Kettritz Ralph
CORPORATE SOURCE: Medical Faculty of the Charite, Department of Nephrology and Hypertension, Franz Volhard Clinic at the Max Delbruck Center for Molecular Medicine, HELIOS-Klinikum-Berlin, Germany.
SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2005 May) Vol. 19, No. 7, pp. 816-8. Electronic Publication: 2005-03-08.
Journal code: 8804484. E-ISSN: 1530-6860.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 29 Apr 2005
Last Updated on STN: 23 Dec 2005
Entered Medline: 22 Dec 2005

AB The effect of fever on **neutrophils** has not been explored. We tested the hypothesis that fever-like temperature spikes affect **neutrophil** signaling and function. Prior 60 min, 42 degrees C heat exposure inhibited p38 MAPK, ERK, **PI3-Kinase**/Akt, and NF-kappaB activation in TNF-alpha-challenged suspended **neutrophils**. Using pharmacological inhibitors and an inhibitory peptide transduced into **neutrophils** by a HIV-TAT sequence, we found that p38 MAPK and NF-kappaB mediate TNF-alpha-mediated delayed **apoptosis** in suspended **neutrophils**. Heat exposure (39-42 degrees C) did not affect constitutive **apoptosis** but abrogated TNF-alpha-delayed **apoptosis** in these suspended cells. In contrast, adhesion-dependent functions were not inhibited. Furthermore, we found that heat exposure neither blocked p38 MAPK, ERK, and NF-kappaB activation in **neutrophils** on fibronectin nor prevented delayed **apoptosis** by TNF-alpha when cells interacted with fibronectin. Above and beyond **apoptosis**, TNF-alpha initiated NF-kappaB-dependent gene transcription. Heat exposure blocked this effect in suspended **neutrophils** but not in **neutrophils** on fibronectin. Finally, we show that beta2-integrins, which are not necessary for TNF-alpha-induced NF-kappaB activation at 37 degrees C, transduce costimulatory signals allowing NF-kappaB activation after heat exposure. The effect could protect circulating **neutrophils** from TNF-alpha activation, while not interfering with activation of adherent **neutrophils**. Fever could make **neutrophils** more parsimonious.

L5 ANSWER 6 OF 25 MEDLINE on STN

ACCESSION NUMBER: 2005670483 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16306804
TITLE: Cardioprotection with adenosine A2 receptor activation at reperfusion.
AUTHOR: Xu Zhelong; Mueller Robert A; Park Sung-Sik; Boysen Philip G; Cohen Michael V; Downey James M
CORPORATE SOURCE: Department of Anesthesiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA.. zxu@aims.unc.edu
CONTRACT NUMBER: HL-20648 (NHLBI)
HL-50688 (NHLBI)
SOURCE: Journal of cardiovascular pharmacology, (2005 Dec) Vol. 46, No. 6, pp. 794-802. Ref: 83
Journal code: 7902492. ISSN: 0160-2446.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 21 Dec 2005
Last Updated on STN: 29 Dec 2005
Entered Medline: 28 Dec 2005

AB Pre-ischemic treatment is seldom possible in the clinical setting of acute myocardial infarction. Thus, to successfully save myocardium from infarction, it is required that protective interventions must be effective when applied after ischemia has begun or at the onset of reperfusion. Unfortunately, in spite of a large body of experimental data showing that various interventions are cardioprotective at reperfusion, no specific therapy has yet been established to be clinically applicable. However, recent data from several laboratories have shown that adenosine and its analogues given at reperfusion can markedly protect the heart from ischemia/reperfusion injury. While the experimental data suggest that factors such as adenosine A2 receptor activation, anti-**neutrophil** effect, attenuation of free radical generation, increased nitric oxide (NO) availability, activation of the **PI3-kinase**/Akt pathway and ERK, prevention of mitochondrial damage, and anti-apoptotic effects may be involved in the protective effect of adenosine or its analogues, the exact receptor subtype(s), the detailed signaling mechanisms, and interaction between those individual factors are still unknown. A definite answer to these unsolved problems will offer insights into the mechanisms of cardioprotection at reperfusion, and will be critical for developing a successful therapeutic strategy to salvage ischemic myocardium in patients with acute myocardial infarction.

L5 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:417048 CAPLUS
DOCUMENT NUMBER: 143:90811
TITLE: Clozapine prevents **apoptosis** and enhances receptor-dependent respiratory burst in human **neutrophils**
AUTHOR(S): Vargas, F.; Rivas, C.; Perdomo, H.; Rivas, A.; Ojeda, L. E.; Velasquez, M.; Correia, H.; Hernandez, A.; Fraile, G.
CORPORATE SOURCE: Laboratorio de Fotoquimica, Facultad de Ciencias de la Salud, Universidad de Carabobo-Nucleo Aragua, Venez.
SOURCE: Pharmazie (2005), 60(5), 364-368
CODEN: PHARAT; ISSN: 0031-7144
PUBLISHER: Govi-Verlag Pharmazeutischer Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was undertaken to determine if the antipsychotic drug clozapine (CLZ) in the concentration range 2-50 μM can rescue polymorphonuclear cells (**PMNs**) from undergoing **apoptosis**

. Our results indicate that 20 μM CLZ can rescue **PMNs** both from UVB-accelerated (28.0% vs. 45.9% for control without CLZ; P < 0.05) and from spontaneous (35.8% vs. 57.6%; P < 0.05) **apoptosis** whereas 50 μM CLZ could rescue **PMNs** from spontaneous (34.3% vs. 57.6%; P < 0.05) **apoptosis** only. Furthermore, since **apoptosis** has been reported to involve the impairment of **PMN** function, we evaluated the effects of CLZ on respiratory burst in UVB-irradiated and in unirradiated **PMNs**. When 20 or 50 μM CLZ-pretreated **PMNs** were aged in a culture during 4 h, the luminol-dependent chemiluminescence (CL) response was 3-fold (P < 0.01) and 2.5-fold (P < 0.05) increased, resp., by subsequent exposure to serum opsonized zymosan (OZ). When 50 μM-pretreated **PMNs** were either UVB-irradiated or unirradiated, the CL response was 2.6-fold (P < 0.05) and 3.3-fold (P < 0.05) increased, resp., after subsequent exposure to formyl-methionyl-leucyl-phenylalanine (fMLP). In contrast, the degree of enhancement was negligible upon subsequent exposure to ionomycin or phorbol myristate acetate (PMA). When incubation times were extended up to 22 h, the CL response induced by OZ in 20 μM CLZ-treated **PMNs** had a 4.9-fold increase (P < 0.001). This priming effect could be reverted when 20 μM CLZ-treated **PMNs** (aged 4 h in culture) were coincubated for 5 min with the protein tyrosine kinase inhibitor genistein as well as with the phosphatidylinositol 3-kinase (PI3-K) inhibitor wortmannin. These findings suggest that CLZ primes respiratory burst and prevents **PMN apoptosis** as a consequence of tyrosine phosphorylation- and PI3-K activation-dependent signal transduction pathways.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 8 OF 25 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2005328015 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15793629
TITLE: Postconditioning--A new link in nature's armor against myocardial ischemia-reperfusion injury.
AUTHOR: Vinten-Johansen J; Zhao Z-Q; Zatta A J; Kin H; Halkos M E; Kerendi F
CORPORATE SOURCE: The Cardiothoracic Research Laboratory, Carlyle Fraser Heart Center, 550 Peachtree Street N.E., Atlanta, Georgia 30308-2225, USA.. jvinten@emory.edu
CONTRACT NUMBER: HL069487 (NHLBI)
HL64886 (NHLBI)
SOURCE: Basic research in cardiology, (2005 Jul) Vol. 100, No. 4, pp. 295-310. Electronic Publication: 2005-03-30. Ref: 105
Journal code: 0360342. ISSN: 0300-8428.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200510
ENTRY DATE: Entered STN: 28 Jun 2005
Last Updated on STN: 12 Oct 2005
Entered Medline: 11 Oct 2005

AB Reperfusion injury is a complex process involving several cell types (endothelial cells, **neutrophils**, and cardiomyocytes), soluble proinflammatory mediators, oxidants, ionic and metabolic dyshomeostasis, and cellular and molecular signals. These participants in the pathobiology of reperfusion injury are not mutually exclusive. Some of these events take place during the very early moments of reperfusion, while others, seemingly triggered in part by the early events, are activated within a later timeframe. Postconditioning is a series of brief mechanical interruptions of reperfusion following a specific prescribed algorithm applied at the very onset of reperfusion. This algorithm lasts only from 1 to 3 minutes depending on species. Although associated with

re-occlusion of the coronary artery or re-imposition of hypoxia in cell culture, the reference to ischemia has been dropped. Postconditioning has been observed to reduce infarct size and **apoptosis** as the "end games" in myocardial therapeutics; salvage of infarct size was similar to that achieved by the gold standard of protection, ischemic preconditioning. The cardioprotection was also associated with a reduction in: endothelial cell activation and dysfunction, tissue superoxide anion generation, **neutrophil** activation and accumulation in reperfused myocardium, microvascular injury, tissue edema, intracellular and mitochondrial calcium accumulation. Postconditioning sets in motion triggers and signals that are functionally related to reduced cell death. Adenosine has been implicated in the cardioprotection of postconditioning, as has e-NOS, nitric oxide and guanylyl cyclase, opening of K(ATP) channels and closing of the mitochondrial permeability transition pore. Cardioprotection by postconditioning has also been associated with the activation of intracellular survival pathways such as ERK1/2 and **PI3 kinase** - Akt pathways. Other pathways have yet to be identified. Although many of the pathways involved in postconditioning have also been identified in ischemic preconditioning, some may not be involved in preconditioning (ERK1/2). The timing of action of these pathways and other mediators of protection in postconditioning differs from that of preconditioning. In contrast to preconditioning, which requires a foreknowledge of the ischemic event, postconditioning can be applied at the onset of reperfusion at the point of clinical service, i.e. angioplasty, cardiac surgery, transplantation.

L5 ANSWER 9 OF 25 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2006:222745 BIOSIS
DOCUMENT NUMBER: PREV200600221732
TITLE: Expression and distribution of signal regulatory protein alpha in human **neutrophils**.
AUTHOR(S): Stenberg, Asa [Reprint Author]; Oldenborg, Anna; Frazier, William A.; Sehlin, Janove; Oldenborg, Per-Arne
CORPORATE SOURCE: Umea Univ, Dept Integr Med Biol, SE-90187 Umea, Sweden
SOURCE: Journal of Leukocyte Biology, (2005) No. Suppl. S, pp. 37-38.
Meeting Info.: 38th Annual Meeting of the Society-for-Leukocyte-Biology. Oxford, ENGLAND. September 21 -24, 2005. Soc Leukocyte Biol.
CODEN: JLBIE7. ISSN: 0741-5400.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Apr 2006
Last Updated on STN: 5 Apr 2006

L5 ANSWER 10 OF 25 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2005185855 EMBASE
TITLE: Activation of **PI3-kinase**/PKB contributes to delay in **neutrophil** **apoptosis** after thermal injury.
AUTHOR: Hu Z.; Sayeed M.M.
CORPORATE SOURCE: Z. Hu, Dept. of Physiology, Loyola Univ. Medical Center, 2160 S. First Ave., Maywood, IL 60153, United States. zhu1@luc.edu
SOURCE: American Journal of Physiology - Cell Physiology, (2005) Vol. 288, No. 5 57-5, pp. C1171-C1178. .
Refs: 43
ISSN: 0363-6143 CODEN: AJPCDD
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English

SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 May 2005
Last Updated on STN: 19 May 2005

AB **Neutrophil apoptosis** is delayed under trauma and/or sepsis injury conditions. The molecular mechanism for the delay in **apoptosis** has not been well defined. We investigated whether activation of phosphatidyl inositol 3-kinase (**PI3-kinase**)/PKB signaling pathway contributes to the delay in **neutrophil apoptosis** with thermal injury. Rats were subjected to burns (30% total body surface area, 98°C for 10 s), and euthanized 24 h later. Blood **neutrophils** were isolated with the use of Ficoll gradient centrifugation and cultured for the indicated time periods. **Apoptosis** was determined using annexin V and PI labeling and flow cytometry. NF-κB activation was examined using gel mobility shift assay and confocal microscopy. Expression levels of inhibitory **apoptosis** proteins (IAPs), including cellular IAP1 (cIAP1), cIAP2, X-linked IAP (XIAP), and survivin, and Bcl-2 family members such as Bcl-xl and Bad, were determined by Western blot analysis and/or RT-PCR, real-time PCR. The results showed that in culture, the decrease, in **apoptosis** of **neutrophils** from thermally injured rats was prevented in the presence of **PI3-kinase** inhibitors wortmannin and LY-294002. There was upregulation of PKB and Bad phosphorylation and NF-κB activation in N-formyl-L-methionyl-L-leucyl-L-phenylalanine- stimulated **neutrophils** from thermally injured rats compared with the sham injured group. Increased Bad phosphorylation and NF-κB activation were also attenuated by wortmannin. Bcl-xl expression in **neutrophils** was upregulated with thermal injury and inhibited in the presence of wortmannin. However, the expression of IAP family members was neither affected by thermal injury nor inhibited by wortmannin. These data suggest that the delay in **neutrophil apoptosis** with thermal injury is partly caused by activation of **PI3-kinase**/PKB signaling and NF-κB, which appeared to be related to the increased Bcl-xl expression and phosphorylation of Bad, but not IAP expression.

L5 ANSWER 11 OF 25 BIOSIS
ACCESSION NUMBER: 2005:235909 BIOSIS
DOCUMENT NUMBER: PREV200510020974
TITLE: The effect of fever-like temperatures on **neutrophil** signaling.
AUTHOR(S): Salanova, Birgit; Choi, Mira; Rolle, Susanne; Wellner, Maren; Scheidereit, Claus; Luft, Friedrich C.; Kettritz, Ralph [Reprint Author]
CORPORATE SOURCE: Wiltbergstr 50, D-13125 Berlin, Germany
kettritz@fvk.charite-buch.de
SOURCE: FASEB Journal, (MAR 2005) Vol. 19, No. 3.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jun 2005
Last Updated on STN: 23 Jun 2005

AB The effect of fever on **neutrophils** has not been explored. We tested the hypothesis that fever-like temperature spikes affect **neutrophil** signaling and function. Prior 60 min, 42 degrees C heat exposure inhibited p38 MAPK, ERK, **PI3-Kinase**/Akt, and NF-kappa B activation in TNF-alpha-challenged suspended **neutrophils**. Using pharmacological inhibitors and an inhibitory peptide transduced into **neutrophils** by a HIV-TAT sequence, we found that p38 MAPK and NF-kappa B mediate TNF-alpha-mediated delayed **apoptosis** in suspended **neutrophils**. Heat exposure (39-42 degrees C) did not affect constitutive **apoptosis** but abrogated TNF-alpha-delayed **apoptosis** in these suspended cells.

In contrast, adhesion-dependent functions were not inhibited. Furthermore, we found that heat exposure neither blocked p38 MAPK, ERK, and NF-kappa B activation in **neutrophils** on fibronectin nor prevented delayed **apoptosis** by TNF-alpha. when cells interacted with fibronectin. Above and beyond **apoptosis**, TNF-alpha initiated NF-kappa B-dependent gene transcription. Heat exposure blocked this effect in suspended **neutrophils** but not in **neutrophils** on fibronectin. Finally, we show that beta 2-integrins, which are not necessary for TNF-alpha-induced NF-kappa B activation at 37 degrees C, transduce costimulatory signals allowing NF-kappa B activation after heat exposure. The effect could protect circulating **neutrophils** from TNF-alpha. activation, while not interfering with activation of adherent **neutrophils**. Fever could make **neutrophils** more parsimonious.

L5 ANSWER 12 OF 25 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2004262919 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15162444
TITLE: The survival effect of TNF-alpha in human **neutrophils** is mediated via NF-kappa B-dependent IL-8 release.
AUTHOR: Cowburn Andrew S; Deighton John; Walmsley Sarah R; Chilvers Edwin R
CORPORATE SOURCE: Respiratory Medicine Division, Department of Medicine, University of Cambridge School of Clinical Medicine, Addenbrooke's and Papworth Hospitals, Cambridge, GB.. asc32@hermes.cam.ac.uk
SOURCE: European journal of immunology, (2004 Jun) Vol. 34, No. 6, pp. 1733-43.
Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200407
ENTRY DATE: Entered STN: 27 May 2004
Last Updated on STN: 30 Jul 2004
Entered Medline: 29 Jul 2004

AB The capacity of cytokines to modulate **neutrophil apoptosis** is thought to be a major factor influencing the resolution of granulocytic inflammation. We have previously shown that the late survival effect of TNF-alpha in human **neutrophils** involves activation of both NF-kappa B and phosphoinositide 3-kinase (**PI3-kinase**) pathways. In this study, we address how these pathways integrate to prevent cell death. In human **neutrophils**, TNF-alpha (200 U/ml) induced rapid I kappa B-alpha degradation, NF-kappa B activation and IL-8 release (31.8+/-5.4 pg/10(5) cells/2 h), whereas GM-CSF (10 ng/ml) stimulated an equivalent IL-8 release (26.5+/-4.5 pg/10(5) cells/2 h) without enhanced I kappa B-alpha degradation or NF-kappa B activation compared to control. Importantly, inhibition of **PI3-kinase** did not modify TNF-alpha -induced I kappa B-alpha degradation, yet fully inhibited the survival effect of both cytokines. Inhibition of I kappa B-alpha phosphorylation, **PI3-kinase** or ERK1/2 activation blocked IL-8 release by both cytokines. Blocking IL-8 activity by inhibiting its synthesis or by using a neutralizing antibody enhanced the early pro-apoptotic effect of TNF-alpha and inhibited its late survival effect without affecting GM-CSF-induced survival. These data suggest that cross-talk between NF-kappa B and **PI3-kinase** pathways in TNF-alpha -stimulated **neutrophils** results from NF-kappa B/ERK1/2-dependent IL-8 production which acts in an autocrine manner to drive **PI3-kinase**-dependent survival. In contrast, GM-CSF-mediated survival does not involve NF-kappa B activation or IL-8 release.

L5 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:458242 CAPLUS
DOCUMENT NUMBER: 141:223482
TITLE: The importance of resolution of inflammation in the pathogenesis of ANCA-associated vasculitis
AUTHOR(S): Harper, L.; Williams, J. M.; Savage, C. O.
CORPORATE SOURCE: Division of Medical Sciences, University of Birmingham, Birmingham, B15 2TT, UK
SOURCE: Biochemical Society Transactions (2004), 32(3), 502-506
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The primary small-vessel systemic vasculitides are disorders that target small blood vessels, inducing vessel wall inflammation, and are associated with the development of anti-**neutrophil** cytoplasmic antibodies. Multiple organs are attacked, including the lungs and kidneys. Increasing knowledge of pathogenesis suggests that the antibodies activate **neutrophils** inappropriately, leading to endothelial and vascular damage. Cytokines, such as tumor necrosis factor, can facilitate damage by priming the **neutrophils** and activating endothelial cells. **Apoptosis** of infiltrating **neutrophils** is also disrupted by anti-**neutrophil** cytoplasmic antibody activation, and removal of these effete cells occurs in a pro-inflammatory manner, promoting persistent inflammation. The autoimmune response may be promoted by aberrant phagocytosis of apoptotic **neutrophils** by dendritic cells. Understanding the pathogenesis can help to rationalize existing therapies and indicate new approaches to therapy.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:458233 CAPLUS
DOCUMENT NUMBER: 141:223910
TITLE: Gene profiling of in vitro and in vivo models of delayed **neutrophil apoptosis**: a common pathway?
AUTHOR(S): O'Neill, A.; Greenan, M. C.; Doyle, B.; Fitzpatrick, J. M.; Watson, R. W. G.
CORPORATE SOURCE: Department of Surgery, Conway Institute, University College Dublin, Mater Misericordiae University Hospital, Dublin, 7, Ire.
SOURCE: Biochemical Society Transactions (2004), 32(3), 470-473
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mechanisms responsible for the termination of an inflammatory response include the activation of a genetic program of cellular suicide termed **apoptosis**, which leads to the elimination of the cellular effectors of acute inflammation, particularly the **neutrophil**. However, delays in this response result in the persistence of inflammation and the development of inflammatory disorders. Understanding the mechanism that inhibits the process of cell death may be helpful in the treatment of inflammatory disorders. Inflammatory cytokines have been shown to inhibit **apoptosis** through stabilization of the mitochondria and inhibition of the caspase cascade. To date, how these processes are inhibited remains the central question. The authors hypothesize that the decision for the delay in **neutrophil** **apoptosis** is made through signals delivered on the cell surface, which activate combinations of specific genes that inhibit the cell death

pathway. Gene chip microarray expts. were performed in in vivo and in vitro models of delayed **neutrophil apoptosis**. Anal.
has yielded changes in a large number of genes involved in inflammation, metabolism, signaling, mitochondrial function and **apoptosis**. A number of genes have been identified as suitable targets responsible for the regulation of **neutrophil apoptosis** and their
expression was confirmed by real-time PCR and explored at the level of the protein. Their functional role in the apoptotic response is now being determined One significant finding is that the gene patterns of delay in vitro and in vivo appear to be different, indicating the possibility for different pathways regulating the delay in **neutrophil apoptosis**.

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